Renal risk markers and cardiovascular disease

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Chapter 7

Urinary albumin excretion predicts cardiovascular and non-cardiovascular mortality in the general population

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Accepted for publication in Circulation

Abstract

Background— For the general population the clinical relevance of an increased urinary albumin excretion rate is still debated. Therefore, we examined the relationship between urinary albumin excretion and all-cause mortality and mortality caused by cardiovascular (CV) disease and non-CV-disease in the general population.

Methods and Results— In the period 1997-1998, all inhabitants of the city of Groningen, The Netherlands, aged between 28 and 75 years (n = 85,421), were sent a postal questionnaire collecting information regarding risk factors for CV disease and CV morbidity, and a vial to collect an early morning urine sample for measurement of urinary albumin concentration (UAC). The vital status of the cohort was subsequently obtained from the municipal register, and the cause of death from the Central Bureau of Statistics. Of these 85,421, 40,856 subjects (47.8%) responded, and 40,548 could be included in the analysis. During a median follow-up period of 961 days (maximum 1,139 days), 516 deaths with known cause were recorded. We found a positive dose-response relation between increasing UAC and all-cause mortality. A higher UAC increased the risk of both CV and non-CV of death after adjustment for other well-recognised CV risk factors, the increase being significantly higher for CV mortality than for non-CV mortality ($P = 0.014$). A twofold increase in UAC was associated with a relative risk of 1.29 for CV mortality (95%CI, 1.18-1.40) and 1.12 (1.04-1.21) for non-CV mortality.

Conclusions— Urinary albumin excretion is a predictor of all-cause mortality in the general population. The excess risk was more attributable to death from CV causes, independent from the effects of other CV risk factors, and the relationship was already apparent at levels of albuminuria currently considered to be normal.

Introduction

Epidemiological and experimental data show that high levels of urinary albumin excretion are associated with an increased incidence of all cause, and in particular cardiovascular (CV) mortality. This evidence comes from observations in high-risk patients like diabetics, hypertensives, elderly, and in elderly subjects with a history of established CV disease[1-8]. The link between urinary albumin excretion and atherosclerotic disease is suggested to be found in dysfunction of the endothelium and its sequela. However, the relevance of urinary albumin excretion as a risk indicator in the general population is controversial. The few published studies are either small, have relied on retrospectively collected data, or are coming from groups of subjects who were referred because of suspected disease[5-7]. The greater morbidity and poorer health status in these selected patient populations hamper the generalisation of the results to the population at large. In the present study we therefore address the question of a relationship between urinary albumin excretion and all-cause mortality and both CV and non-CV mortality, in a large cohort selected from the general population.

Methods

Design and study population

The PREVEND (Prevention of REnal and Vascular ENd stage Disease) study is designed to prospectively investigate the natural-course of increased levels of urinary albumin excretion and its relation with renal and CV disease in a large cohort drawn from the general population. Details of this protocol have been described elsewhere[9,10]. In the period 1997-1998 all inhabitants of the city of Groningen (The Netherlands), between the age of 28 to 75 years, in total 85,421 subjects, were sent a postal questionnaire and a vial to collect an early morning urine sample in which urinary albumin concentration (UAC) was measured, and altogether 40,856 subjects (47.8%) responded. The one-page questionnaire collected information on the presence of established risk factors for CV disease and documented CV morbidity. Subjects were considered diabetic when they positively answered the question whether they had a physician diagnosis of diabetes, regardless of the type of anti-diabetic treatment. Those who reported taking antihypertensive or lipid lowering medication were regarded as hypertensive and hyperlipidaemic, respectively. Subjects were classified as smokers if they reported smoking or having smoked cigarettes during the previous 5 years. A history of myocardial infarction or stroke was considered present if the subject reported having been hospitalised for at least three days due to that condition. A family history of CV disease was considered present if at least one first-degree relative

had documented angina pectoris, myocardial infarction or stroke before the age of 65 years.

All participants gave written informed consent. The PREVEND study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki.

Urinary albumin measurements

Urinary albumin excretion was measured as the urinary albumin concentration (UAC) in a morning urine sample. UAC was determined by a commercial immunoturbidimetry assay with sensitivity of 2.3 mg/L and inter- and intra-assay coefficients of variation of 4.4% and 4.3%, respectively (BNII, Dade Behring Diagnostica). Microalbuminuria was defined as a UAC between 20 to 200 mg/L and macroalbuminuria > 200 mg/L[11].

Mortality data

From the time of recruitment, the vital status of the participants was checked through the municipal register. The cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by a physician from the Central Bureau of Statistics. Causes of death were coded according to the tenth revision of the International Classification of Diseases (ICD-10). Cause specific end points used in the analyses were CV disorders, and the remaining codes those from non-CV causes.

Survival time for participants was defined as the period from the date of the urine collection of the participant to the date of death from any cause, or September 2000 until which date information regarding specific causes of death follow up information was available. If a person had moved to an unknown destination, the date on which the person was dropped from the municipal registry was used as census date.

Statistical analysis

To study the effects of albumin excretion on mortality we fitted Cox proportional hazards models to the data. Two competing death causes were distinguished: CV and non-CV. Apart from UAC the following available explanatory variables for CV and non-CV death were entered in the regression analysis: sex, age, presence of diabetes mellitus, use of antihypertensive drugs, use of lipid-lowering drugs, smoking, family history of CVD, previous myocardial infarction and stroke. We used competing risk analysis, which allows to compare effects of explanatory variables on either CV or non-CV death[12]. P-splines were employed to explore the functional form of effects of continuous variables age and UAC. Results are summarised by hazard (risk) ratios (RR) with confidence intervals based on ro-

bust standard error estimates, by plotting adjusted hazard ratio as a function of UAC, and by plotting cause-specific cumulative incidence functions for specific covariate values. Five percent (two-sided) *P*-values were used as the nominal level of statistical significance. We used the statistical package S-Plus 6 (2001, Insightful Co, Seattle, USA) for the analysis.

Results

The total population sample comprised 40,856 subjects. During the follow-up period, 518 cases were recorded. From these 518 deaths, 178 were classified as CV, and 340 as non-CV, using the cause of death obtained from death certificates. The non-CV mortality group included 231 malignant neoplasms, 10 were classified as diabetes, and 99 cases were classified as various. For 73 participants the time on study was not available. Urine samples could technically not be analysed in 235 subjects. Two of these participants died from a non-CV cause. In total, 40,548 participants from whom 516 were died were available for the analysis. The median follow-up time was 961 days (maximum of 1,139 days).

Table 1 shows the baseline characteristics of the study cohort at the time of inclusion stratified into CV and non-CV mortality. Those who died were older, more likely being male and more likely to have a history of diabetes, hypertension, hyperlipidemia, smoking or a (parental) history of CV disease than those who survived. Moreover, those who died from CV causes had the highest prevalences of these risk factors.

Urinary albumin excretion and mortality

There was a clear dose response relation between UAC and all-cause mortality. Crude incidence rates of all-cause mortality per 1000 person years were 3.5 (95%CI, 3.1-3.9) for patients with a UAC below 10 mg/L, 4.5 (95%CI, 3.6-5.5) for subjects with UAC levels of 10 to 20 mg/L, 11.2 (95% CI, 9.1-13.7) for subjects with UAC levels of 20 to 200 mg/L, and 29.1 (95%CI, 19.3-43.7) for those with levels of 200 mg/L or higher (*P* for trend < 0.001).

Table 2 summarises the results of the Cox regression analysis adjusted for age and sex. Both CV and non-CV deaths were found to be associated with presence of diabetes mellitus, hyperlipidemia, smoking, myocardial infarction and UAC level. CV-deaths were also associated with a history of stroke. The effect of age on the log-hazard was found to be linear, the effect of UAC was linear after logarithmic transformation of UAC. A higher UAC increased the risk of both types of death, the increase being significantly higher for the CV deaths ($P = 0.009$). The inclusion in the regression model of the other cardiovascular risk factors did not substantially alter the relation between UAC and CV and non-CV death.

Table 1. Characteristics of the total study group

Characteristic	Mortality status				Missing cases (n)
	Total population	Alive	CV death	Non-CV death	
N	40,548	40,032	178	338	
Age,yrs, P50 (P5 – P95)	48 (30-71)	48 (30-71)	68 (45-74)	65 (43-74)	
Male gender,%	45.6	45.4	66.8	59.5	
Diabetes, %	2.6	2.5	7.9	10.1	129
Hypertension, %	11.2	11.0	38.1	`22.3	1368
Hyperlipidaemia, %	4.7	4.7	11.4	6.1	1744
Family history of CVD, %	32.1	32.1	43.2	29.8	2213
History or actual smoking, %	42.2	42.1	47.7	54.1	252
Myocardial infarction, %	3.0	2.9	18.0	11.1	887
History of stroke, %	0.8	0.8	8.6	2.4	697
Morning UAE, mg/L, P50 (P5–P95)	6.1 (2.3–28.7)	6.1 (2.3–27.9)	8.6 (2.3–240)	7.7 (2.3–104)	
Microalbuminuria, %	7.2	7.0	22.5	16.0	

Table 2. Cox regression: cause-specific hazard (risk) ratios

Variable	Adjusted for age and sex				Mutually adjusted for multiple risk factors			
	RR	(95%-CI)	*P*		RR	(95%-CI)	*P*	
Female sex					0.60	(0.49-0.74)	< 0.001	
Age (per 10 years)					2.58	(2.32- 2.84)	< 0.001	
Hyperlipidemia	0.88	0.62-1.24)	0.460		0.60	(0.42-0.85)	0.004	
Diabetes	1.89	1.35-2.65)	<0.001		1.62	(1.15-2.29)	0.006	
Myocardial infarction	1.78	1.31-2.32)	<0.001		1.84	(1.37-2.46)	<0.001	
Smoking								
Cardiovascular	1.83	1.33-2.51)	<0.001		1.65	(1.19-2.27)	0.002	
Non-cardiovascular	2.60	2.07-3.27)	<0.001	0.073#	2.49	(1.97-3.16)	<0.001	(0.039)#
Stroke								
Cardiovascular	5.49	3.07-9.81)	<0.001		4.01	(2.20-7.30)	<0.001	
Urinary albumin excretion (doubling)								
Cardiovascular	1.35	(1.24-1.46)	<0.001		1.29	(1.18-1.40)	<0.001	
Non-cardiovascular	1.17	(1.09-1.25)	<0.001	0.009#	1.12	(1.04-1.21)	0.002	(0.014)#

Comparison of effect on CV mortality vs. non-CV mortality

In this mutually adjusted model, a twofold increase in UAC, i.e. from 5 to 10 mg/L or 20 to 40 mg/L, was associated with a 1.29 higher risk for CV death and 1.12 for non-CV death ($P = 0.014$). Smokers tended to have an increased risk for non-CV death ($P = 0.039$). The effects of the level of UAC on the cause-specific hazards for CV and non-CV mortality, adjusted for all the risk factors as shown in Table 2, are presented in Figure 1. The solid line curves corresponding to the log-linear functional form lie within the dotted CI-curves. This supports reasonability of the chosen model, although the (P-spline based) CI-curves obviously do not exclude the existence of a more complex functional relation. For CV deaths the increase in risk associated with an increase in UAC is steeper than that for non-CV deaths.

To show the effects of UAC within the currently used reference ranges, cause-specific cumulative incidence functions using the Cox model were calculated for two UAC levels well below the lower border of the definition of microalbuminuria. The curves represent the cumulative incidence functions of CV and non-CV mortality for a non-hypertensive, non-hyperlipidemic, non-diabetic, non-smoking 50 years old male without a history of myocardial infarction or stroke with UAC levels set equal to the 25th percentile (3.8 mg/L), and to the 75th percentile (9.8 mg/L).

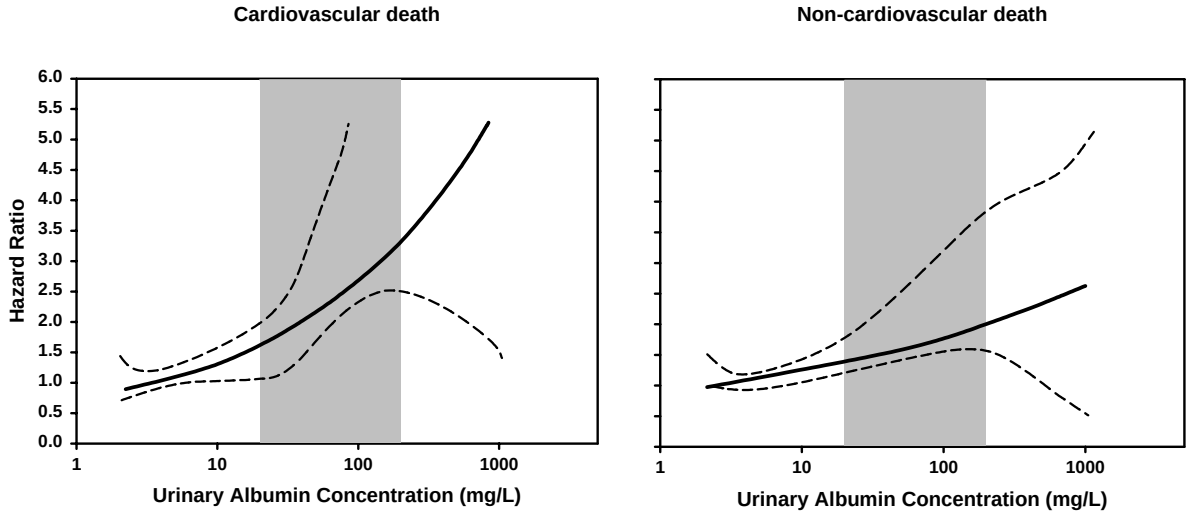

Figure 1. Adjusted effect of UAE on hazard function. Solid lines show the estimated relation when log-hazard is modelled as a linear function of log(UAC). The dotted lines are 95% confidence limits for a more general functional relation as estimated by P-splines. The grey area represents the upper and lower limit of the current definition of microalbuminuria (20-200 mg/L).

The 2-year cumulative incidence of CV mortality for a UAC of 3.8 mg/L is 0.11% and for a UAC of 9.8 mg/L 0.15%, whereas for non-CV mortality these figures are 0.21% and 0.24%, respectively (Figure 2).

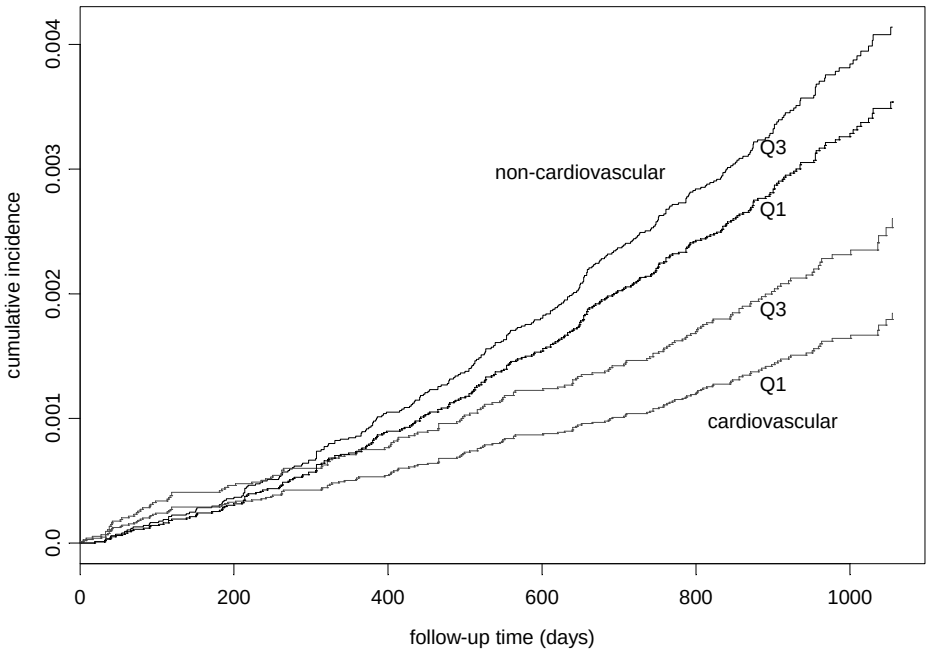

Figure 2. Cause-specific cumulative incidence functions of CV and non-CV mortality for non-hypertensive, non-hyperlipidemic, non-diabetic, non-smoking 50 years old males without a history of myocardial infarction or stroke with UAC levels set equal to the 25th percentile (3.8 mg/L), and to the 75th percentile (9.8 mg/L).

Discussion

This is the first study to show that urinary albumin excretion is a strong predictor of all-cause mortality in the general population at large. The excess risk was significantly more attributable to death from CV causes than to death from non-CV causes and independent from the effects of various well-recognised CV risk factors. Importantly, the relationship between UAE level and mortality was already apparent at levels of albuminuria currently considered to be normal.

Microalbuminuria is associated with an increased risk for renal and CV morbidity and all-cause mortality in diabetic patients, patients with hypertension, and in elderly subjects[1-8]. We found a stronger relation between albuminuria and mortality from CV causes when compared with non-CV mortality in an unselected cohort derived from the population at large. In view of this finding, Albuminuria appears to be a marker of generalised vascular disease and indicates an

incremental risk for CV mortality not only in CV compromised subjects. The precise underlying mechanism is unknown. It is possible that the glomerular albumin leak reflects a widespread atherosclerotic mediated capillary vasculopathy[13-15]. Dysfunction of the coagulation and fibrinolysis systems has also been suggested as a possible link between microalbuminuria and CV disease. In diabetic and non-diabetic subjects microalbuminuria has been associated with changes in von Willebrand factor, fibrinogen, thrombomodulin, and PAI-1[16-18]. Urinary albumin excretion, however, is associated with several other risk factors that may themselves be linked with mortality. These include e.g. diabetes mellitus, hyperglycemia, hypertension, renal dysfunction, dyslipidemia, hyperhomocysteinemia, dietary protein, smoking, and markers of an acute phase response. A critical question within this context is, whether the relation of urinary albumin excretion and mortality is due to an association of urinary albumin excretion with other predictors of mortality. If albuminuria and the other prognostic factors share a common, causal pathway, adjustment for these factors may attenuate the relation between albuminuria UAE and mortality. However, even after adjustment for these factors, albuminuria remains relatively strong predictive after full adjustment, suggesting an independent additive component in the relation between albuminuria and mortality from CV causes.

We also observed an association, although less strong, between albuminuria and non-CV mortality. The incidence of non-CV mortality could mostly be attributed to death due to malignant neoplasm's. An elevated urinary albumin excretion in patients with malignancies has been reported before[19]. Interestingly, although the precise underlying mechanism is unknown, it has been speculated that in this type of patients the increased urinary albumin loss appears to be more an isolated renal phenomenon than related with endothelial dysfunction because a normal endothelial function was observed, as demonstrated by the transcapillary escape rate of albumin which suggests an overall unaffected capillary permeability.

This study adds considerable data to the available information on urinary albumin excretion as a vascular risk factor because we have used the full range of UAC in studying the relationship with mortality and did not cluster UAC-levels into several categories. Several objections could be raised to categorizing UAC, including: (1) a step function is biologically implausible because estimating risk of categories ignores the possibility that actual risk varies smoothly with the exposure of the risk factor; (2) high risk individuals will be submerged in a pool of lower-risk members, thereby diluting the effect size; (3) there may be significant loss of power, especially when the effects are concentrated at the end of the UAC scale, and, (4) cut off point bias may be introduced in the case cut-off points are selected to maximize effect size.

It has been suggested in selected patient populations, that even modestly raised albuminuria values, within what hitherto has been considered the normal range, are associated with a future risk for CV events[3,5,20]. Our finding of a dose-response relationship between UAC and the risk of mortality extends such a suggestion to the general population. Therefore, we suggest that the lower limit defining a "pathological" albuminuria seems appropriate.

Our study has a number of limitations and to appreciate the findings some issues need to be addressed. We have measured urinary albumin excretion concentration only once and without correcting for potential variability in urine concentration. In addition, we were unable to perform detailed measurements of the CV risk factors. Self-reported histories have limitations because a certain degree of misclassification and therefore bias may occur. As we do not expect this misclassification to be related to the risk factors or to the morning urinary albumin measurements themselves, misclassification would dilute the estimated effect, which is to make the estimated RR closer to one. Therefore, our analysis may have underestimated the true association between urinary albumin excretion and mortality. The relatively short follow-up could have masked some of the long-term health hazards of an increased urinary albumin excretion. The current large population based study is not characterised by a high participation rate and hence could be subject to selection bias. However, the finding that close to 40 percent of all deaths in our study were classified as due to CV disease, which is in line with previous prospective studies of subjects of the general population, favours acceptable generalisibility[21].

We conclude from this large prospective cohort study that albuminuria is an important marker for both CV and non-CV mortality. The use of UAC as a screening tool is made more feasible by commercially available more sensitive assays, which also in the lower ranges appear to be reliable. There may be an important clinical role for albuminuria in CV disease screening, analogous to that of blood pressure and lipid screening. Because albuminuria is a modifiable risk marker, the current observation may lead to new therapeutic strategies in the prevention of CV disease.

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